Pure Appl. Chem., Vol. 80, No. 5, pp. 1135–1140, 2008.
doi:10.1351/pac200880051135

γ-Methylidene-δ-valerolactones as a coupling partner for cycloaddition: Palladium-catalyzed [4+3] cycloaddition with nitrones*

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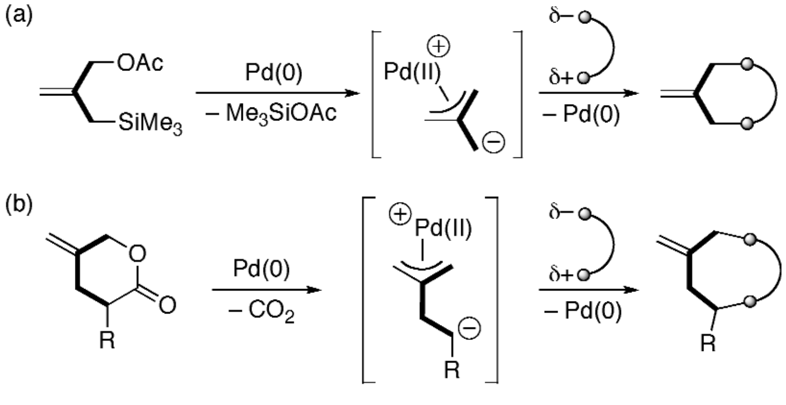
Abstract: A new type of reagent, γ-methylidene-δ-valerolactones, has been devised, which acts as a four-carbon unit in a Pd-catalyzed cycloaddition reaction through the formation of a 1,4-zwitterionic species. The utility has been demonstrated in the context of stereoselective [4+3] cycloaddition with nitrones to provide highly functionalized 1,2-oxazepines, including the asymmetric variant with high enantioselectivity.

Keywords: cycloaddition; nitrones; palladium catalyst; asymmetric catalysis.

INTRODUCTION

Intermolecular cycloadditions catalyzed by transition-metal complexes are useful methods for convergent synthesis of cyclic materials [1]. The development of a new and efficient intermolecular cycloaddition reaction is, therefore, of high value in organic chemistry. In this context, Trost described the use of palladium–trimethylenemethane (TMM) complexes as a 1,3-dipole-like three-carbon unit in the formation of a cyclic framework almost 30 years ago (Scheme 1a) [2]. Since then, this method has been applied to the construction of a variety of cyclic compounds [3], and some asymmetric variants have also been reported [4]. Herein we introduce a new type of reagent, γ-methylidene-δ-valerolactones,



Scheme 1

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*Paper based on a presentation at the 14th International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-14), 2–6 August 2007, Nara, Japan. Other presentations are published in this issue, pp. 807–1194.

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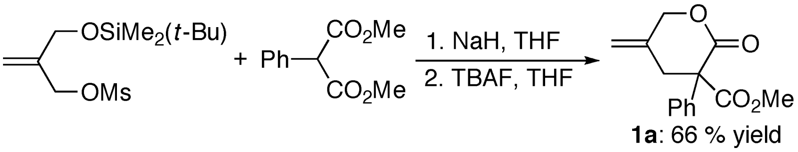
which serves as a four-carbon unit in the Pd-catalyzed cycloaddition through the formation of a 1,4-zwitterionic species (Scheme 1b) [5], and demonstrate their utility in the [4+3] cycloaddition with nitrones to provide highly functionalized 1,2-oxazepines [6], including the asymmetric variant with high enantioselectivity.

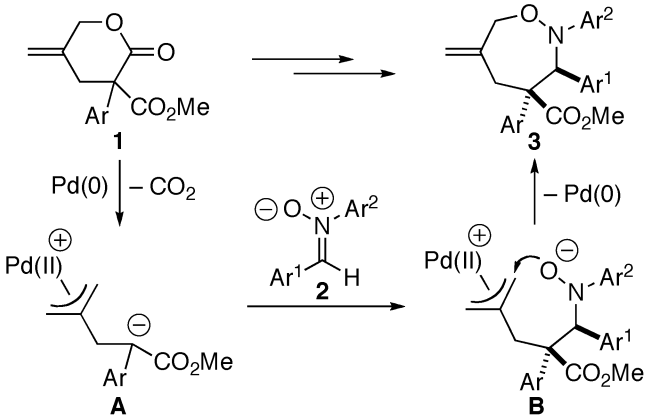
CYCLOADDITION OF γ-METHYLIDENE-δ-VALEROLACTONES WITH NITRONES

In an initial investigation, we prepared γ-methylidene-δ-valerolactone **1a** as a model reagent for our study in two steps from known compounds as shown in Scheme 2, and examined its utility for a [4+3] cycloaddition reaction with nitrone **2a** in the presence of 5 mol % of Pd catalyst at 40 °C (Table 1). The reaction proceeded smoothly by the use of PPh_3 as a ligand, giving the desired 1,2-oxazepine **3aa** in 95 % yield as a mixture of two diastereomers (72/28; entry 1). The use of other ligands such as $P(Oi\text{-}Pr)_3$ and phosphoramidite **4** [7] also gave **3aa** in high yield (97–99 % yield; entries 2 and 3), and high diastereoselectivity (90/10) was achieved with ligand **4**. Other ligands such as $t\text{-}Bu_2P(o\text{-}PhC_6H_4)$, $P(Ot\text{-}Bu)_3$, and $P(OPh)_3$ were not very effective, giving **3aa** in <30 % yield. Under the conditions with **4** as the ligand, several other γ-methylidene-δ-valerolactones undergo cycloadditions with **2a** as well to give the corresponding 1,2-oxazepines in high yield with good to excellent diastereoselectivity (87/13–94/6; entries 4–7). Unfortunately, however, lactones **1** with alkyl substituents are not suitable reagents under the present reaction conditions. The cycloaddition also proceeds with nitrones having a substituted aryl group at their electrophilic carbon atoms with high diastereoselectivity (92/8–94/6; entries 8–10).



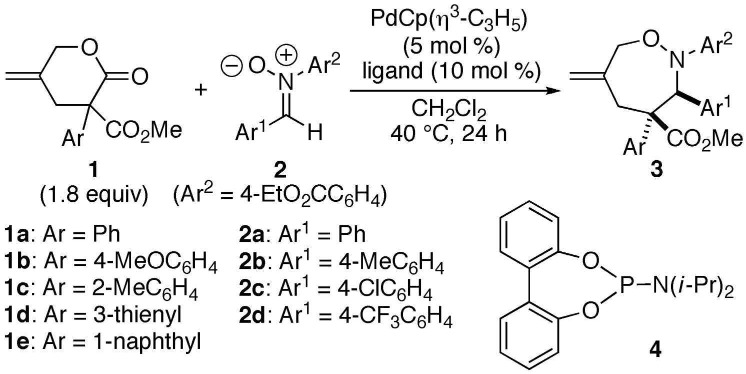
Scheme 2

A proposed catalytic cycle of this process is illustrated in Scheme 3. Thus, oxidative addition of the allyl ester moiety of **1** to Pd(0), followed by decarboxylation [8,9], gives 1,4-zwitterionic species **A**. The anionic carbon of **A** then attacks the electrophilic carbon of **2** to give intermediate **B**, which undergoes a ring-closure through a nucleophilic attack of the oxygen atom to the π-allylpalladium moiety, leading to the formation of 1,2-oxazapine **3** along with regeneration of Pd(0).



Scheme 3

Table 1 Pd-catalyzed [4+3] cycloaddition of γ-methylidene-δ-valerolactones **1** with nitrones **2**.

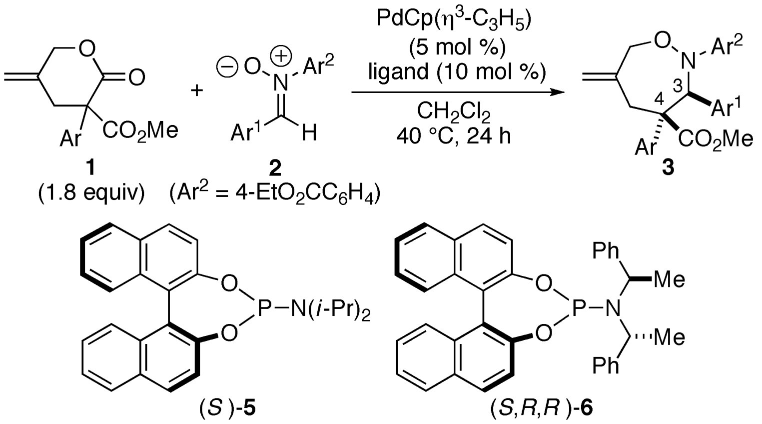


Entry	1	2	Ligand	Product	Yield (%)[a]	dr[b]
1	**1a**	**2a**	PPh_3	**3aa**	95	72/28
2	**1a**	**2a**	$P(Oi\text{-}Pr)_3$	**3aa**	97	78/22
3	**1a**	**2a**	**4**	**3aa**	99	90/10
4	**1b**	**2a**	**4**	**3ba**	95	93/7
5	**1c**	**2a**	**4**	**3ca**	62	87/13
6	**1d**	**2a**	**4**	**3da**	92	91/9
7	**1e**	**2a**	**4**	**3ea**	96	94/6
8	**1e**	**2b**	**4**	**3eb**	77	92/8
9	**1e**	**2c**	**4**	**3ec**	98	93/7
10	**1e**	**2d**	**4**	**3ed**	98	94/6

[a] Combined yield of two diastereomers.
[b] Determined by ^1H NMR.

Because the step from **A** to **B** in Scheme 3 creates two contiguous tertiary and quaternary stereocenters, it would be desirable to conduct this reaction in an asymmetric fashion. On the basis of the ligand effect described in Table 1, we employed chiral phosphoramidite ligand (*S*)-**5** [10] in the reaction of **1a** with nitrone **2d**. Under these conditions, cycloadduct **3ad** was obtained in high yield (98 % yield, dr = 85/15) and the enantioselectivity of the major diastereomer was 71 % ee (Table 2, entry 1). By changing the nitrogen substituents from isopropyl to (*R*)-1-phenylethyl (ligand (*S*,*R*,*R*)-**6**) [10,11], higher enantioselectivity was observed (83 % ee; entry 2). Other γ-methylidene-δ-valerolactones such as **1b** and **1e** also provide the cycloadducts with nitrones **2** with high efficiency in the presence of ligand (*S*,*R*,*R*)-**6** (84–96 % ee; entries 3–6). The absolute configuration of **3ec** (entry 6) was determined to be (3*S*,4*R*) by X-ray crystallographic analysis as shown in Fig. 1.

Table 2 Pd-catalyzed asymmetric [4+3] cycloaddition of **1** with **2**.



Entry	1	2	Ligand	Product	Yield (%)[a]	dr[b]	ee (%)[c]
1	**1a**	**2d**	(*S*)-**5**	**3ad**	98	85/15	71
2	**1a**	**2d**	(*S*,*R*,*R*)-**6**	**3ad**	98	81/19	83
3	**1b**	**2d**	(*S*,*R*,*R*)-**6**	**3bd**	99	86/14	84
4	**1e**	**2d**	(*S*,*R*,*R*)-**6**	**3ed**	98	80/20	96
5[d]	**1e**	**2b**	(*S*,*R*,*R*)-**6**	**3eb**	99	70/30	89[e]
6	**1e**	**2c**	(*S*,*R*,*R*)-**6**	**3ec**	89	72/28	88[f]

[a] Combined yield of two diastereomers.

[b] Determined by ^{1}H NMR.

[c] Ee of the major diastereomer (determined by chiral HPLC).

[d] The reaction was conducted with 10 mol % of catalyst for 48 h.

[e] The minor diastereomer was 91 % ee.

[f] The minor diastereomer was 89 % ee.

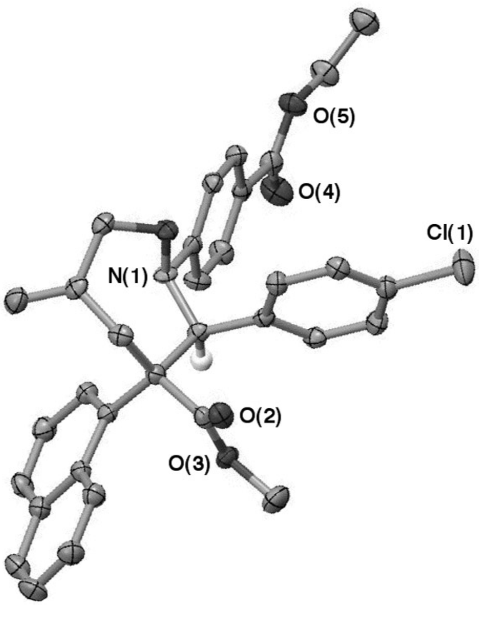
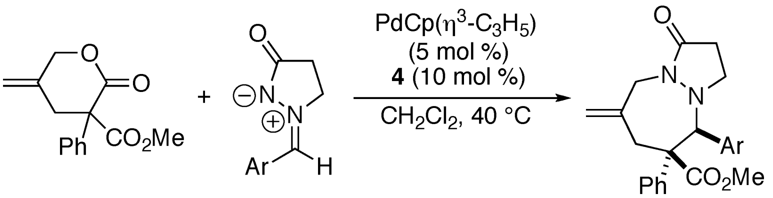


Fig. 1 X-ray structure of **3ec** with thermal ellipsoids drawn at the 50 % probability level (Flack parameter = –0.01(6)).

CYCLOADDITION OF γ-METHYLIDENE-δ-VALEROLACTONES WITH OTHER PARTNERS

The present catalysis using regents **1** is not limited to the couplings with nitrones. For example, **1a** underwent a cycloaddition with azomethine imine **7** [12,13] to give the corresponding [4+3] cycloadduct (**8**) with dr = 87/13, and the major diastereomer was isolated in 79 % yield (Scheme 4). In addition, the reaction of **1a** with methyl acrylate in the presence of P(*o*-Tol)$_3$ as the ligand gave the corresponding [4+2] cycloadduct (**9**) in 83 % yield with dr = 84/16 (Scheme 5).

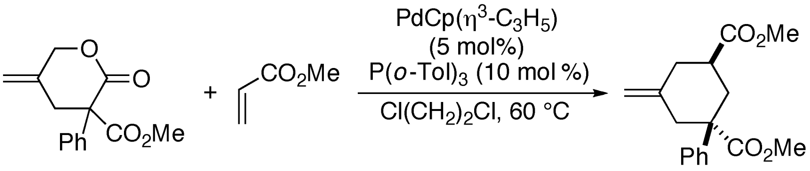


1a
(1.8 equiv)

7
(Ar = 4-$CF_3C_6H_4$)

8: dr = 87/13
major: 79 % yield

Scheme 4



1a
(1.8 equiv)

9: 83 % yield
(dr = 84/16)

Scheme 5

CONCLUSIONS

In summary, we have described the development of γ-methylidene-δ-valerolactones as a new class of reaction partner in the Pd-catalyzed cycloaddition reaction. These reagents act as a four-carbon unit in a cyclic framework by forming a 1,4-zwitterionic species, and we have demonstrated their utility in the context of stereoselective [4+3] cycloaddition with nitrones, including the results of the asymmetric variant. Future studies will explore further application of these reagents to various other transition-metal-catalyzed cycloaddition reactions.

ACKNOWLEDGMENTS

Support has been provided in part by a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science and Technology, Japan (21 COE on Kyoto University Alliance for Chemistry).

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